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## **PATHOLOGY AND MEDICINAL PLANT TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE**

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### **Abstract**

Gastroesophageal reflux disease (GERD) is a prevalent chronic disorder characterized by the backflow of acidic gastric contents into the esophagus due to lower esophageal sphincter (LES) dysfunction. This condition causes esophageal mucosal damage, leading to symptoms such as heartburn and chest pain, and is associated with increased risks of severe complications, including esophageal adenocarcinoma.

### **Aims:**

To review the current state of GERD management and assess the potential of photochemical plant-based treatments as alternatives to conventional therapies.

### **Methods:**

A comprehensive literature review was performed to describe the status of GERD in detail while focusing on the emerging role of plant-based therapies in GERD management.

### **Results:**

Traditional treatments for GERD are effective but often come with side effects and limitations. Plant-based treatments, particularly those with photochemical properties, are potential

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complementary therapies. Preliminary data suggest these alternatives may improve symptom management and patient outcomes.

### **Conclusions:**

While standard treatments for GERD are widely used, their limitations necessitate exploring alternative options. Photochemical plant-based therapies offer a promising, supplementary approach, pending further validation through research and clinical trials.

**Keywords:** *Medicinal plant, Gastroesophageal reflux disease, pathophysiology, Esophagitis.*

## **1. Introduction**

Gastroesophageal reflux disease (GERD), more commonly referred to as heartburn, is a globally widespread condition (1). It can affect individuals from various age groups and both sexes. The worldwide frequency of the disease is estimated to be between 8% to 33% (2), which, according to the American Gastroenterological Association, is 1/3 of the population (3). Both gastroenterologists and general care physicians regard it as one of the most frequently occurring conditions (4). The digestive system in a healthy body proceeds from the mouth to the esophagus and right away to the stomach. However, in people with GERD, there is a disruption in this path, causing stomach acids to flow backward from the stomach into the esophagus, throat, and mouth (3) GERD has many definitions. An updated one describes it as “a condition which develops when the reflux of stomach contents causes troublesome symptoms (i.e., at least two heartburn episodes per week) and/or complications.”(5). The occurrence of potentially deadly consequences can be caused by GERD, even if the condition itself is not lethal (6). Based on the symptoms produced, it can be classified into two major types: erosive type, which is associated with esophageal mucosal damage, and non-erosive reflux disease, which encompasses symptoms lacking endoscopic indications of injury to the esophageal mucosa (7).

Conditions resulting from erosive reflux disease include reflux esophagitis, reflux stricture, Barrett esophagus, and esophageal adenocarcinoma. In contrast, non-erosive reflux disease is linked to ailments in which the patient reports pain in their chest, heartburn, or regurgitation. Yet, there is no sign of esophageal mucosal damage. In addition to conditions that have a suggested relationship with disease (such as inflammation of the pharynx, sinusitis, idiopathic pulmonary fibrosis, and

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recurrent otitis media), extra-esophageal disorders connected to heartburn include disorders that are known to be associated with GERD (such as dental damage, inflammation of the larynx, coughing, and asthma) (8). It has been demonstrated to have a significant detrimental effect on a person's quality of life concerning their health and a significant negative economic and societal cost (1).

## 2. Symptoms

Damage to the mucosa resulting from aberrant stomach acid reflux into the esophagus, mouth, lungs, or larynx is one of the symptoms of GERD. Heartburn and/or regurgitation of acid occur at least a single time per week as symptoms. It should be noted that GERD diagnosis has limitations based solely on patient symptoms because some individuals have endoscopic signs of the disease (e.g., Barrett's esophagus or esophagitis) but do not show symptoms. In contrast, other patients show symptoms but no objective signs of the disease. The significant financial burden associated with GERD is a result of both the illness's high prevalence and the expensive cost of medications that lower acid levels. GERD symptoms can be classified into three primary categories: extraesophageal, atypical, and usual. Symptoms tend to be more severe after eating a meal, are usually exacerbated by lying down, and are often alleviated by taking acid-lowering medications. Common GERD symptoms include acid reflux and heartburn, which have a poor sensitivity but a high specificity (4). Achalasia, gastritis, dyspepsia, gastroparesis, and peptic ulcer disease are among the disorders in the differential diagnosis that may be signs of GERD. Still, they may also coexist with unusual symptoms such as nausea, bloating, belching, and dyspepsia. Finally, a few extraesophageal symptoms persist, such as laryngitis, asthma, teeth erosions, and coughing (9). Currently accepted theories suggest that these symptoms may be caused by refluxate microaspiration or a vagally mediated reaction triggered by exposure to distal esophageal acid. The esophagobronchial reflex, the process via which distal esophageal acid exposure may cause coughing, is thought to be mediated by the common vagal innervation of the esophagus and cough reflex. In the context of GERD, extraesophageal symptoms should not be automatically attributed solely to GERD, particularly in the absence of typical symptoms. Symptoms of GERD have a significant influence on quality of life and health. According to a study, a lower quality of life in terms of physical and mental health is associated with reflux symptoms that persist even after

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receiving proton pump inhibitor (PPI) therapy. When deciding on managing a patient's disease, it is advised to consider behavioral and psychological aspects, notably when the patient has decreased well-being and persistent reflux symptoms even after receiving PPI treatment (10). Therefore, to prevent adverse impacts on quality of life and a host of consequences, it is crucial to identify, diagnose, and treat individuals with GERD appropriately (4).

### **3. Risk Factors**

GERD risk factors are many and have been hypothesized. The most well-established links are those involving alcohol consumption, GERD in the family, and body mass index (8). Pregnancy, scleroderma and neuropathies-related delayed and disturbed esophageal motility, and surgical vagotomy are additional potential risk factors. Numerous foods and medications have been linked to promote mucosal irritation or reduce the pressure of the lower esophageal sphincter (LES). Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), nitroglycerin, blockers of calcium channels, anticholinergics, antidepressants, sildenafil, albuterol, and glucagon are a few medications that may be linked to the onset of GERD symptoms. Foods like chocolate, caffeine, and heavy meals may worsen acid reflux symptoms. Research on these contributions, however, is inconsistent. There exists a contradiction in the studies concerning the association between GERD and tobacco smoking. There is little to no evidence linking carbonated soft drinks, overindulging, and eating quickly (11).

### **4. Pathophysiology**

The etiology of gastric reflux disease is complex. Acid secretion, inflammation, and oxidative stress are the pathophysiologic elements of GERD (12). GERD is predisposed by several variables, such as defective mucosal resistance, delayed stomach emptying, aberrant peristalsis, inadequate esophageal acid clearance, and increased intraabdominal pressure. When the lower esophageal sphincter (LES) relaxes, the esophagus becomes more vulnerable to stomach contents such as bile, pepsin, small intestinal fluid, and pancreatic secretions in addition to gastric acid. These compounds can potentially damage the esophagus's mucosa (11). After meals, an area of unbuffered gastric acid builds up in the proximal stomach, just next to the gastroesophageal connection, called an "acid pocket," where acid reflux into the esophagus may be prevented. The upper esophageal sphincter relaxes in response to activation of the stomach's stretch receptors,

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which is mediated by the vago-vagal reflex system (13). When the lower esophageal sphincter briefly relaxes, stomach contents escape into the esophagus. Although small quantities of acid reflux are acceptable, gastroesophageal reflux is deemed abnormal if it persists over an extended period at  $\text{pH} < 4$ . Long-term exposure of the esophagus to digestive enzymes and acid from gastric fluid or duodenal contents regurgitated into the stomach (such as bile salts) can cause and encourage irritation of the esophageal mucosa, leading to symptoms and morphological abnormalities. Because the mucosal tissues of the esophagus have limited inherent resistance to reflux, the integrity of the anti-reflux barrier, which is made up of the crural diaphragm and the lower esophageal sphincter is essential for preventing reflux-related symptoms and injury (14). A hiatus hernia is a substantial risk factor for GERD because it may reduce the lower esophageal sphincter's ability to prevent stomach contents from entering the esophagus (13).

## **5. Complications**

### **5.1. Esophagitis**

Esophagitis, or inflammation of the distal esophageal mucosa resulting in erosions, affects around 18% to 25% of individuals with GERD symptoms (15). Erosive esophagitis, a significant GERD side effect marked by ulcers and damage to the esophageal mucosa, is one of the main symptoms. Patients with erosive esophagitis typically exhibit the classic signs of GERD, even though they may not have any symptoms at all. The most widely used method for grading esophagitis severity is the Los Angeles Esophagitis Classification System. Mucosal breaks' circumferential severity, height, location, and quantity determine the Los Angeles system's A, B, C, and D grading system (8).

Although erosive reflux esophagitis may present with symptoms like GERD, it may also present with none. Once endoscopy reveals esophagitis, the degree of mucosal erosive areas is graded from A to D according to the Los Angeles classification system. Less than five-millimetre erosions are classified as grade A, five-millimetre erosions as grade B, erosions between the tops of two or more mucosal folds that involve less than seventy-five percent of the circumference as grade C, and erosions involving seventy-five percent or more of the circumference as grade D. Long-term care is necessary for individuals with esophagitis because quitting PPI medication

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usually causes recurrence. However, after the drug is proven to work therapeutically, The recommended daily dosage must be lowered to the lowest amount the patient can handle (15).

## **5.2. Structure**

Fibrotic scarring brought on by acidic exposure to the esophagus can result in the development of peptic esophageal strictures. In untreated patients with erosive esophagitis, the incidence of peptic strictures ranges from 7% to 23% (16). The cause of esophageal strictures is a disturbed healing mechanism and continuous acid irritation that scars the esophagus. Most GERD-related strictures happen at the squamocolumnar junction. Dysphagia and food impaction are common complaints from patients. Taking extra care when swallowing food is necessary to manage esophageal strictures, and esophageal dilatation may be required. When a patient is refusing treatment, injecting corticosteroids into the stricture may be an option. Although stent migration, chest discomfort, bleeding, and esophageal perforation are risks, stricture stenting may be an alternative. Using a PPI to reduce acid production might be beneficial, especially in preventing stricture recurrence (8). Dysphagia is frequently observed in patients with esophageal stricture. Continuous long-term PPI medication is part of the treatment, along with endoscopic balloon dilatation, which may need to be repeated but effectively treats esophageal strictures in over 80% of cases. If scarring returns after many dilatations, dilatation plus corticosteroid injection may be an option; however, the studies supporting this strategy are tiny, have little follow-up, and are inconclusive (17).

## **5.3. Barrett Esophagus**

One GERD consequence that may turn cancerous is Barrett's esophagus. Barrett's esophagus predisposes esophageal adenocarcinoma. Typically, the stratified squamous epithelium lining the distal esophagus is replaced by meta-plastic columnar epithelium in Barrett's esophagus. Histologically, mucus-secreting goblet cells are present in metaplastic columnar epithelium—the development of the metaplastic epithelium results from long-term exposure to stomach acid and other refluxed materials. Male sex, age above 50, obesity, smoking, hiatal hernia, and Caucasian racial background are additional risk factors. A diet rich in fruits and vegetables, NSAID use, and H pylori infection in the stomach may, for unknown reasons, protect against Barrett's esophagus.

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While dysplasia may be evident in Barrett's esophageal reflux disease, not all patients with Barrett's esophagus have dysplastic alterations. Every year, approximately 0.25% of people with Barrett's esophagus go on to develop esophageal cancer. Patients with high-grade dysplasia and extended segments of the afflicted esophagus are more likely to progress to esophageal cancer (8).

The precursor lesion to esophageal adenocarcinoma, Barrett's esophagus, can be brought on by GERD. Barrett's esophagus, which is not dysplastic, has a modest absolute risk of esophageal cancer, but dysplasia increases that risk significantly. According to a second meta-analysis involving 20 papers and 74943 Barrett esophageal patients, male sex, older age, tobacco use, longer Barrett mucosal segment, and central obesity were the primary risk variables for tumor advancement (15).

#### **5.4. Esophageal Adenocarcinoma**

Barrett's esophageal development is linked to esophageal cancer in cases of GERD (15). Over the past forty years, there has been a significant rise in esophageal adenocarcinoma, especially in Western nations. The global incidence rate of this disease is 1.1 cases per 100,000 person-years for men and 0.3 cases per 100,000 person-years for women (18). The 5-year survival rate is less than 20%. Nonetheless, due to the tumor's rarity in the general population, even while GERD patients have a higher relative chance of developing esophageal adenocarcinoma, the absolute risk is minimal. It is debatable if GERD medication lowers the risk of esophageal adenocarcinoma (15).

#### **6. Treatment**

Treatment for gastric reflux disease (GERD) consists of medication, lifestyle changes, and long-term surgical alternatives. Reducing weight and elevating the head of the bed are two effective lifestyle modifications. Patients are also recommended to avoid lying down for three hours after eating and to avoid trigger foods like chocolate, coffee, and alcohol (19). It is especially advised for those who have gained weight recently to lose weight. Proton-pump inhibitors (PPIs), which are more effective than histamine-receptor antagonists (H2RAs), are the mainstay of medical therapy for acid control. Since most patients with erosive reflux disease (ERD) return after stopping PPI therapy, maintenance therapy at the lowest effective dose is advised. In treating non-erosive reflux disease (NERD), H2RA therapy or on-demand PPI medication may be helpful.

Compliance and appropriate dosage should be addressed first in PPI-refractory GERD. If symptoms don't go away, a different PPI can be used, or the dosage can be. Using baclofen or adding H2RAs at night may also be beneficial. For individuals who refuse to take their medicine, are intolerant of it, or have symptoms that are not improving medically, surgical options such as laparoscopic fundoplication or bariatric surgery are taken into consideration (20).

GERD symptoms can be well alleviated with a laparoscopic fundoplication, while some patients may still need medication after the procedure. Gas bloat syndrome and dysphagia are possible side effects. An alternative with encouraging outcomes is the LINX Reflux Management System, which entails putting a magnetic wristband over the lower esophageal sphincter (LES). There has been little progress with endoscopic treatments, and several methods have been taken off the market because they don't work. There have been conflicting outcomes with transoral incisionless fundoplication; nonetheless, research is still being conducted to enhance endoscopic GERD therapy choices. It is advised that individuals with GERD who are morbidly obese (BMI > 35 kg/m<sup>2</sup>) undergo gastric bypass surgery, preferably Roux-en-Y gastric bypass. This technique lowers the risk of long-term mortality and comorbidities associated with obesity in addition to more effectively addressing GERD causes. In this population, sleeve gastrectomy and adjustable gastric banding are less effective than Roux-en-Y gastric bypass in improving GERD results (20).

About 20–40% of GERD patients do not respond to PPI medications (20). Even with PPI drugs, specific GERD therapeutic needs remain unfulfilled. Furthermore, because of PPI refractoriness, up to 40%–55% of daily PPI users experience persistent symptoms (11). Potassium-competitive acid blockers (P-CABs) competitively inhibit the potassium-binding site of H<sup>+</sup>, K<sup>+</sup>-adenosine triphosphate ATPase. While this class of medications has a long history, two P-CABs, Vonoprazan and Revaprazan, have only recently been licensed for clinical usage in Japan and Korea, respectively (11). P-CABs overcome several PPI's disadvantages and restrictions. A growing amount of evidence indicates that they offer a significant additional benefit when taken as main or adjunctive medications (to standard treatment), especially in treating symptoms that do not improve with PPI therapy (11). Furthermore, studies have demonstrated that vonoprazan's acid-inhibitory impact is more substantial than PPIs' (20).

## 7. Medicinal Plants



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*Asiatica Artemisia*: in a study exploring the effect of *Artemisia asiatica* extract (DA-9601), the findings showed that DA-9601 was significantly more effective than ranitidine in treating reflux esophagitis. DA-9601 reduced the number of ulcers, decreased esophageal wall thickness, and improved inflammation and mucosal recovery, showing superior healing effects. In contrast, ranitidine did not significantly reduce ulceration and inflammation or promote mucosal regeneration. The findings suggested that DA-9601 offers a more comprehensive approach by addressing both acid-induced and oxidative damage, making it a superior treatment option (21).

*Myrtus communis*: Administration of an aqueous extract of *Myrtus communis* fruit significantly reduced dyspeptic and reflux ratings in a randomized controlled experiment (22). Rats with stomach ulcers were demonstrated to benefit from the preventive effects of several fruit extracts. Additionally, the extracts decreased the overall acidity and amount of gastric juice.

*Olea Europea*: Giving olive oil for two to six months to post-gastrectomy patients with highly symptomatic duodeno-gastric reflux who did not respond to traditional treatments either eliminated the patients' symptoms or significantly reduced them (23).

*Cydonia oblonga* (quince): When a syrup made from the fruit of this plant was given to kids with GERD, their symptoms significantly improved over time. Still, the decline was not statistically significant compared to the control group. Quince syrup continued to work even after stopping the use of omeprazole for two weeks (22).

*Morus alba*: In rats treated with leaf extract from the plant before GERD was induced, the amount of mucus on the stomach wall increased. H<sup>+</sup>-K<sup>+</sup>-ATPase and plasma histamine levels both sharply dropped. By reducing lipid peroxidation and raising the concentration of antioxidant enzymes, *morus alba* extract showed antioxidant activity (12).

*Panax quinquefolium*: Rats receiving *Panax quinquefolium* first showed a dose-dependent reduction in lipid peroxidation, increased antioxidant status, and a notable decrease in the extent of tissue damage caused by RE. However, whereas omeprazole effectively reduced mucosal damage, it did not show any antioxidant activity. The expression of genes encoding proteins associated with acute inflammation, such as cytokine-induced neutrophil chemoattractant 2 (CINC-2) and intercellular adhesion molecule 1 (ICAM-1), was also considerably reduced by

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*Panax quinquefolium*. It did not affect monocyte chemotactic protein 1 (MCP-1), a marker of ongoing inflammation (12).

*Rubus spp.* (black raspberry): Black raspberry dietary supplementation did not alter cellular antioxidant or lipid peroxidation levels in a brief experiment, including the production of GERD in an animal model of esophagoduodenal anastomosis compared to the control diet. Furthermore, it did not influence the onset of Barrett's esophagus or the degree of esophagitis (12).

*Salvia miltiorrhiza*: By causing rats' lower esophageal sphincters (LES) to contract tonic, *Salvia miltiorrhiza* appears to help treat gastroesophageal reflux disease. It was discovered that the underlying mechanism of this contractile action is the extracellular Ca (2+) influx pathway (12).

*Atropa belladonna*, sometimes referred to as a deadly nightshade, has an alkaloid in its leaves and roots that blocks muscarinic receptors. In human trials, this anticholinergic herb has been demonstrated to reduce relaxation of the lower esophageal sphincter and reflux episodes. Rather than having a local effect on the LES, atropine influences the brain stem. People with GERD are advised to use only whole-plant extracts as purified atropine has more negative effects. 8–10 drops of a 1:5 tincture of *belladonna* leaf is usually taken with each meal. Although possible, mild dry mouth does not warrant changing the dosage. On the other hand, symptoms such as confusion or impaired vision that appear after consuming the plant may indicate an overdose. The herbal intake should be stopped if these symptoms occur and should not return till they do. After that, it can be given again at half the original dose (24).

*Brassica oleracea* (cabbage): The outcomes of an experimental study establish that giving chronic and severe GERD patients plant-based fresh raw cabbage juice extract resulted in a 100% cure. In its natural state, the composition of cabbage may help prevent or treat acid reflux. Varied factors, such as a person's work environment, lifestyle, and level of anxiety, may contribute to varied compositions of acid reflux disease (GERD). However, all of the patients in the experiment experienced a cure from fresh, raw cabbage juice extract, which went beyond these differences in composition and reduced GERD (3).

*Euphorbia hirta*: this plant is widely known for its hypoglycemic, antiasthmatic, antifungal, antibacterial, anti-inflammatory, galactogenic, antidiarrheal, antioxidant, and antimalarial properties. The effects of a whole plant extract and flavonoids from *E. hirta* on gastric

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reflux disease (GERD) in rats were studied. According to the findings, the groups who received both the plant extract and the flavonoids also had higher amounts of stomach wall mucus and significantly lower levels of plasma histamine and H<sup>+</sup> K<sup>+</sup> ATPase. Plant extract and flavonoids increased catalase, reduced glutathione levels, and decreased superoxide dismutase and lipid peroxidation. The potential of *E. hirta* to treat GERD is associated with its antisecretory, gastroprotective, and antioxidant qualities. It also has this property in common with kaempferol, quercetin, rutin, and omeprazole, among other proton pump inhibitors. Standardized *E. hirta* plant extract, which contains kaempferol, rutin, and quercetin, significantly impacted the production of stomach mucus and prevented the discharge of stomach acid. The study results show that treating rats' GERD with an extract from the *E. hirta* plant is beneficial. This demonstrates that the antisecretory and antioxidant qualities of *E. hirta* plants may be responsible for their positive effects, supporting the use of these seeds to treat GERD (25, 26).

### **8. Mechanism of Medicinal Plants**

The antioxidant and anti-inflammatory properties of medicinal herbs are the main underlying processes responsible for their impact on GERD. The following herbal medicines and therapeutic herbs function along these pathways: *Panax quinquefolium*, *Artemisia asiatica*, *Lonicera japonica*, STW 5, *Curcuma longa*, and *Lonicera asiatica*. Additional mechanisms include decreasing gastric acid (*Curcuma longa*, *Morus alba*, acidinol syrup), upregulating the genes encoding proteins involved in acute inflammation, such as ICAM-1 and CINC-2 (*Panax quinquefolium*), and suppressing the pro-inflammatory cytokines TNF- $\alpha$  and IL-1 $\beta$  (STW 5). Anti-secretory medication has not been demonstrated to diminish inflammation or the severity of RE; therefore, it is insufficient to provide comprehensive recovery. An anti-secretory medication that enhances mucosal aging is omeprazole, for instance. Thus, it could not considerably lessen the oxidative stress and inflammatory parameter alterations linked with RE. Anti-inflammatory and antioxidant activity are what most medicinal herbs studied for GERD exhibit, not anti-secretory qualities. The potential benefit of medicinal plants over traditional anti-secretory medicines lies in their ability to treat NERD, an area where PPIs do not exhibit any possible impact. In addition, the therapeutic effects of medicinal plants seem to continue longer than those of traditional anti-secretory drugs. To illustrate, two weeks after stopping, *Cydonia oblonga* remained effective (12).

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## 9. Conclusion

GERD is a chronic condition that carries significant risks if not effectively managed, including serious complications such as Barrett's esophagus, esophageal strictures, and esophageal cancer. Conventional treatment approaches, including pharmacotherapy and lifestyle modifications, effectively control symptoms and prevent disease progression. However, there is a growing interest in complementary therapies, particularly the implication of medicinal plants, which may offer additional therapeutic options.

An integrated approach that combines traditional medical interventions with rigorously validated alternative therapies could provide a more comprehensive treatment strategy for GERD, thereby enhancing patient outcomes and quality of life. Additional research is essential to substantiate the efficacy of these alternative treatments.

### Footnotes.

Ahmed Gad (lecturer of internal medicine) and Ayman Sadek (assistant professor of internal medicine) were the peer reviewers.

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**Authors' contributions**

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